

Pfizer	PF-03049423 - PDE5 inhibitor
<b>Mechanism of Action</b>	<p>Selective, competitive and reversible PDE5 inhibitor  IUPHAR/BPS Guide to pharmacology:  <a href="http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1304&amp;familyId=260&amp;familyType=ENZYME">http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1304&amp;familyId=260&amp;familyType=ENZYME</a>  NCBI Gene data: <a href="http://www.ncbi.nlm.nih.gov/gene/8654">http://www.ncbi.nlm.nih.gov/gene/8654</a>  PDE5 is a cGMP-binding, cGMP-specific phosphodiesterase (PDE), a member of the cyclic nucleotide PDEs family.</p>
<b>Overview</b>	<p>PF-03049423 is an orally available, potent, selective, competitive and reversible PDE5 inhibitor, with IC<sub>50</sub> values of 0.203 and 0.208 nM against the human and rat platelet PDE5 enzymes.</p>
<b>Safety/Tolerability</b>	<p>PF-03049423 was well tolerated in a multiple ascending dose study in healthy young and elderly subjects at doses up to 16 mg (young) and 10 mg (elderly). The most frequent adverse events (AEs) were myalgia and headache, and small (clinically insignificant) decreases in systolic blood pressure were noted. In a double-blind placebo controlled phase 2a study in patients with ischemic stroke enrolled within 72 hours of stroke (NIH Stroke Scale 6–20), the dose was escalated from 1 to 3 to 6 mg per day without major safety concerns. Dosing at 6 mg per day was continued for 90 days in the Proof of Concept phase of the study without significant safety concerns; however, futility on efficacy measures led to early study termination after approximately 180 subjects had been dosed.</p>
<b>Additional Information</b>	<p>Dose-dependent increases in platelet cGMP were noted in phase 1.</p>
<b>Suitable for and Exclusions</b>	<p>13-week rat and dog tox studies have been completed and PF-03049423 was suitable for 90-day dosing in ischemic stroke patients. The Phase 2a stroke study excluded subjects on drugs that could lower BP, including alpha blockers and other PDE5 inhibitors. In the absence of reproductive toxicology data, PF-03049423 is unsuitable for women of child-bearing potential. Excluded Indications: Stroke recovery</p>
<b>Clinical Trials</b>	<p><a href="http://www.clinicaltrials.gov/ct2/show/NCT01208233?term=pfizer+stroke&amp;rank=2">http://www.clinicaltrials.gov/ct2/show/NCT01208233?term=pfizer+stroke&amp;rank=2</a></p>
<b>Additional Characteristics: CNS Penetration/Pediatric Diseases</b>	<p>Data from rat studies indicate that the drug readily diffuses across the blood-brain barrier and suggest that there is no efflux issue affecting the brain disposition of the drug. PF-03049423 showed efficacy in the middle cerebral artery occlusion model of ischemic stroke in rats.</p> <p>PF03049423 is not suitable for evaluation in pediatric studies.</p> <p>PF03049423 failed to demonstrate efficacy in stroke neurorestoration in a phase 2a study.</p>
<b>Publications</b>	<p>None</p>